CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 64-081

BIOEQUIVALENCE REVIEW(S)

DEC 2 0 1994

3

Cefaclor Capsules
250 and 500 mg
AADA #64-081
Reviewer: Moheb H. Makary
WP 64081SDW.994

Biocraft Laboratories, Inc.
Fair Lawn, NJ
Submission Date:
September 8, 1994
September 23, 1994

Review of an Amendment Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has responded to the reviewer's comments made in the review of the May 12, 1994 submissions (single-dose fasting and nonfasting bioequivalence studies for the 500 mg and request for waiver for the 250 mg capsules).

II. Comment #1

The firm was asked to explain the reason of replacement subject #1 with subject #25(if it took place) as indicated in the clinical notes.

Reply to Comment #1

The firm indicated that on January 12, 1994, during the analysis of samples for subject #1, interference from endogenous peaks was observed at or about the retention time of the drug and internal standard peaks. According to the protocol, 24 subjects were to be completed. It was noted that subject #25 had the same dosing sequence as subject #1. On January 27, 1994, samples from subject #25 were analyzed and an interference at the retention time of the drug peak was observed in one of the periods. Since both subject #1 and #25 showed the interference, it was decided to modify the mobile phase (change from pH 2.6 to 2.4) for the separation of the interfering peaks. The samples from subject #1 were reanalyzed on January 31, 1994 with the modified mobile phase and no interference was observed at the retention time of the drug and internal standard. The samples from subject #25 were never reanalyzed with the new mobile phase. The firm has submitted the chromatograms from subject #1, #1 (repeat), and #25.

Furthermore, according to the reviewer's calculations after excluding subject #1 from the pharmacokinetic analysis of the study, the 90% confidence intervals are still within the acceptable range of 80-125 for the log-transformed AUC(0-t), AUCinf and Cmax.

The firm's response to the comment is acceptable.

Comment #2

The firm was asked to include all the assayed data for all subjects in the statistical evaluation of the study.

Reply to Comment #2

The firm has indicated that the samples from subject #25 were not reanalyzed with the modified mobile phase and therefore it was not included in the statistical evaluation of the study.

The firm's response to the comment is acceptable.

Recommendations:

1. The bioequivalence studies under fasting (study #B-07143) and nonfasting (study #B-10143)) conditions conducted by Biocraft Laboratories, Inc., on its Cefaclor 500 mg Capsules, lot #52786, comparing it to Ceclor® 500 mg Pulvules manufactured by Eli Lilly and Company, has been found acceptable by the Division of Bioequivalence. The studies demonstrated that Biocraft's Cefaclor 500 mg Capsules is bioequivalent to the reference product, Ceclor® 500 mg Pulvules, manufactured by Eli Lilly and Company.

2. The dissolution testing conducted by Biocraft Laboratories, Inc., on its Cefaclor Capsules, 250 mg and 500 mg, lots #52869 and 52786, respectively, is acceptable. The formulation for the 250 mg strength is proportionally similar to the 500 mg strength of the test product which underwent bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the 250 mg capsules of the test products is granted. The Division of Bioequivalence deems Cefaclor Capsules 250 mg manufactured by Biocraft Laboratories, Inc., to be bioequivalent to Ceclor® Pulvules 250 mg, manufactured by Eli Lilly and Company.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

[redacted]

4. From the bioequivalence point of view, the firm has met the requirements of the in vivo bioequivalence and the in vitro dissolution testing.

The firm should be informed of the above recommendations.

/S/

Moheb H Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATR /S/
FT INITIALLED RMHATR Date: 12/16/94

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

~~ANDA~~/AADA # 64-081 SPONSOR: Biocraft
DRUG: Cefaclor
DOSAGE FORM: Capsules
STRENGTH(s): 250 mg & 500 mg
TYPE OF STUDY: Single/~~Multiple~~
STUDY SITE: Biossay Laboratories, Houston, TX Fasting/Fed

STUDY SUMMARY: The bioequivalence studies for Cefaclor Capsules, 500 mg are acceptable. Dissolution testings for the 250 mg and 500 mg strengths are acceptable. Waiver for the 250 mg strength is granted.

DISSOLUTION: Dissolution testings are acceptable

PRIMARY REVIEWER: Mahesh H. Mahanj BRANCH: III

INITIAL: /S/ DATE: 12/20/94

BRANCH CHIEF: BRANCH:

INITIAL: /S/ Mhatre DATE: 12/20/94

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: /S/ DATE: 12/20/94

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: /S/ DATE: 12/27/94

1964 THIRTY YEARS QUALITY INTEGRITY SERVICE 1994

biocraft® LABORATORIES, INC.

Noted:
To be reviewed by Bio
Mark Anderson
10/3/94
(referenced disks have gone to reviewer on 10/4 via Mago)

FEDERAL EXPRESS

September 23, 1994

CORPORATE HEADQUARTERS
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7500 Standish Place, Room 150
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ORIG NEW CORRES

AADA 64-081
CEFACLOR CAPSULES, USP, 250 mg and 500 mg

RE: BIOEQUIVALENCE AMENDMENT IN RESPONSE TO TELEPHONE REQUEST, J. GROSS TO M. BORDONI, DATED SEPTEMBER 22, 1994

Dear Staff:

In this amendment we have included diskettes of Protocol #B-07143 (fasting study) and Protocol #B-10143 (food study) for Cefaclor Capsules, USP, 500 mg in AADA 64-081.

Please amend our Application accordingly. Thank you.

Very truly yours,
BIOCRAFT LABORATORIES, INC.

Maurice Bordoni
Director of New Products

SEP 27

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Elmwood Park, NJ 07407
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Cefaclor Capsules USP, 250 mg and 500 mg
AADA 64-081

Biocraft Laboratories, Inc.
Attention: Ms. Nora Bienviaje
18-01 River Road
Fair Lawn, NJ 07410

AUG 18 1994

Dear Ms. Bienviaje:

Reference is made to the *in vivo* bioequivalence studies, waiver request and supporting dissolution data submitted May 12, 1994, for Cefaclor Capsules, USP, 250 and 500 mg.

The Office of Generic Drugs, Division of Bioequivalence has reviewed the referenced material and we have found the single-dose fasted study to be incomplete for the following reasons:

1. On page #196 of the Clinical Findings (Final Report) for Protocol #B-07143, the clinical facility has stated that "The plasma and urine samples for subject #25 were shipped on January 26, 1994, as replacement for subject #1, as requested by the analytical facility."

   The review of this submission noted that subject #1 was included in the analytical and the statistical reports of the study but subject #25 was omitted. Please explain if this replacement took place and the reason for the replacement.

2. All assayed data for all subjects should be included in the statistical evaluation of the study. Please submit this information.

You are required to take an action described under 21 CFR 314.96 which will amend this application.

A representative of the Division of Bioequivalence is available to discuss this letter and to assist with any questions; you may contact Jason A. Gross, Pharm.D., at (301) 594-2290.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

AUG 10 1994

Cefaclor Capsules
250 mg and 500 mg
ANDA # 64-081
Reviewer: Moheb H. Makary
WP 64081SDW.594

Biocraft Laboratories, Inc.
Fair Lawn, NJ
Submission Date:
May 12, 1994

Review of Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has submitted this major amendment in response to the Agency deficiency letters (dated August 16, September 13 and October 16, 1993), which included new bioequivalence studies on its Cefaclor 500 mg capsules.
The firm has submitted two bioequivalence studies under fasting and nonfasting conditions on its reformulated Cefaclor 500 mg capsules to compare the test product with Lilly's Ceclor® 500 mg Pulvules®. The firm also submitted the new formulations for its test products, 500 mg and 250 mg capsules, and their dissolution testing results.

II. Background:

The firm had previously submitted two bioequivalence studies under fasting and nonfasting conditions on its Cefaclor 500 mg capsules (submission dated February 19, 1993). The bioequivalence study under fasting conditions had been found unacceptable by the Division of Bioequivalence. The firm was advised to reformulate its test products.

III. Introduction

Cefaclor is a cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Cefaclor is well absorbed after oral administration in fasting subjects. Total absorption is similar regardless whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23 ug/mL, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted

unchanged in urine within 8 hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with severely reduced renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours.

Currently, Cefaclor is marketed by Eli Lilly under the name Ceclor®, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

III. Report #B-07143 For Single-Dose, Two-Way Crossover Bioavailability Study of Cefaclor 500 mg Capsules Under Fasting Conditions:

Study site:

Analytical site:

Investigators:

Study design:	Single-dose, two period, two-way crossover study.
Subjects:	Twenty-six healthy male volunteers (24 plus two alternates) were enrolled in the study. A total of twenty-five subjects (23 plus two alternates) completed the study.
Selection criteria:	The subjects were between 18 to 35 years of age. All subjects were within ± 10% of their ideal weights as described in the Metropolitan Life Insurance Company, 1983. Only healthy subjects with clinically normal laboratory profiles were enrolled in the study.
Exclusion criteria:	Subjects with a history of chronic alcohol consumption, drug addiction, or serious gastrointestinal, renal, hepatic or cardiovascular disease, tuberculosis, epilepsy, asthma, diabetes, psychosis or glaucoma were excluded from the study. Subjects who have a history of allergic responses to cephalosporins and penicillin were not allowed to participate in the study.

Restrictions: Subjects were instructed not to take any drugs for the 14 days preceding the study and during the course of the study. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine containing products for at least 3 days before dosing and throughout the period of sample collection.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 1x500 mg Cefaclor capsule (Biocraft), lot #52786, lot size capsules. Potency is 95.78% (%CV=0.30) and uniformity of dosage units between 88.7-102.6% (%CV=4.31).

Reference product: B. 1x500 mg Ceclor® Pulvule® (Lilly), lot #6PC28A, Exp. 12/95. Potency is 100.17% (%CV=0.24).

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals were provided at appropriate times thereafter. Water was permitted ad lib. until 1 hour before and 1 hour after dosing.

Blood collection: Blood samples (10 mL) were collected in Vacutainers containing EDTA at 0 (pre-dose) and at the following times after dosing: 0.167, 0.33, 0.5, 0.66, 0.83, 1, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 3.5, 4 and 5 hours. Blood samples were cooled in an ice bath and centrifuged under refrigeration within 10 minutes of sample collection. Plasma samples were stored at - 20°C. The plasma and urine samples were shipped on January 10, 1994, under dry ice to Bioassay Laboratory, Houston, Texas. The plasma samples for subject #25 were shipped on January 26, 1994 as replacement samples for subject #1, as requested by the analytical facility. All samples were acknowledged to be received in frozen condition.

Urine collection: Urine samples were collected at segmented time intervals from 0 to 1, 1 to 2, 2 to 3, 3 to 4, 4 to 6, 6 to 8, 8 to 10, and 10 to 12. After collection, the total volume of the urine for each time interval was determined.

Samples were immediately frozen at -20°C.

Washout period: One week

Assay Methodology: Cefaclor was quantitated in human plasma by using detection. The method was developed and validated at c.

Sensitivity: The lowest non-zero standard was 0.30 ug/mL. At this level, the inter-day precision was 4.79% and accuracy was 104%.

Recovery: The recovery of Cefaclor was determined at each QC concentration level. The recovery was 81.7%, 84.9% and 82.7% for 30.0, 5.00, and 1.00 ug/mL, respectively. The recovery of the internal standard (cephalexin) was determined at 82.3% for 100 ug/mL.

Specificity: No significant baseline disturbance was detected at the retention times of either Cefaclor or internal standard.

Precision: Between-batch precision for quality control samples ranged from 4.3% to 10.1%, and within- batch precision ranged from 1.23% to 3.46%.

Accuracy: Accuracy for quality control samples ranged from 99.2% to 106%.

Stability: Long Term Frozen: The mean change for Cefaclor over the maximum storage period of 77 day at -20°C was -2.2%, +1.2% and +10.8% for 18.0, 6.0 and 0.50 ug/mL, respectively.

In process stability: The results indicated that Cefaclor was stable during the maximum time required for sample processing at room temperature.

Freeze-thaw: Stable after three freeze-thaw cycles. The change was found to be +5.7% and -4.4% for 30.0 and 0.50 ug/mL, respectively.

Statistical Analysis:

Statistical analysis was performed on Cefaclor using the SAS with General Linear Models Procedure (GLM). Analysis of variance was performed on AUCTLQC, AUCinf, Cmax, Tmax, Kel, T1/2 and Cefaclor concentrations at each sampling time point.

IV. In Vivo results:

Twenty-six (26) healthy male volunteers (24 plus two alternates) enrolled in the study. All twenty-six subjects were dosed in period I of the study, and twenty-five subjects (23 plus two alternates) completed the entire clinical portion of the study. Subject #10 dropped before the start of period II due to sore throat, fever and treatment with antibiotics. Alternate subject #26 was chosen to replace subject #10 so that the study would remain balanced within sequence groups. The plasma samples from 24 subjects were assayed for Cefaclor as per the protocol. There were no side effects observed, or adverse events reported, by the subjects, or noted by the staff.

The plasma concentrations and pharmacokinetic parameters for Cefaclor are summarized in Table I.

Table I

Mean Plasma Cefaclor Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 500 mg Capsule Under Fasting Conditions
(N=24)

Time hr	Biocraft Test Product Lot #52786 ug/mL (CV%)	Lilly Reference Product Lot #6PC28A ug/mL (CV%)
0	0	0
0.167	0.08(276.0)	0
0.333	5.78(101.2)	3.71(96.2)
0.500	10.31(63.3)	8.67(57.7)
0.667	11.07(39.2)	9.80(45.5)
0.833	10.10(31.6)	10.01(32.5)
1.000	8.48(27.9)	9.07(27.2)
1.250	6.15(32.6)	6.49(29.4)
1.500	4.64(41.5)	5.28(37.7)
1.750	3.07(35.9)	3.70(40.5)
2.000	2.15(38.6)	2.70(44.6)
2.500	1.18(40.0)	1.41(44.6)
3.000	0.70(40.2)	0.80(44.7)
3.500	0.37(66.4)	0.34(74.8)
4.000	0.11(163.4)	0.13(148.1)
5.000	0	0

				Difference%	90% CI
AUCTLQC	(ug.hr/mL)	13.34(21.5)	13.36(15.9)	- 0.14	95.4-104
AUCinf	(ug.hr/mL)	13.69(20.9)	13.71(15.3)	- 0.13	95.5-104
Cmax	(ug/mL)	13.71(34.1)	12.20(28.5)	+12.35	99.1-126
Tmax	(hr)	0.74(35.2)	0.82(33.7)		
Kel	(1/hr)	1.26(16.6)	1.30(13.7)		

T1/2	(hr)	0.56(17.4)	0.54(13.8)

LNAUCTLQC	93.9-104
LNAUCinf	94.2-104
LNCmax	97.8-125

1. The Cefaclor plasma levels peaked at 0.667 hour and 0.833 hour for the test and the reference products, respectively, under fasting conditions which is in agreement with the literature reported value of 0.75-1 hour for the reference product (Physicians's Desk Reference, 47th ed. 1993:1285-2).

2. For Biocraft's test product, the mean Cmax value is 12.35% higher than the reference product value, the difference is not statistically significant and the 90% confidence interval on log-transformed data is 97.8 - 125.0%.

3. The AUCTLQC and AUCinf values for the test product are almost the same as the AUCTLQC and AUCinf values for the reference product, and the 90% confidence intervals are within the acceptable range of 80-125%

Statistical Evaluation:

No statistically significant differences were detected in products, periods or sequences for any of the pharmacokinetic parameters.

V. Report #B-10143 For Post-Prandial Single-Dose Bioequivalence Study:

Objective: The objective of this study was to compare the bioavailability of Biocraft 500 mg Cefaclor capsules and Lilly's Ceclor® 500 mg Pulvules® under fasting and nonfasting conditions.

Study site:

Investigators: Please see Report #B-07143 above.

Study design: Open-label, randomized, three-way crossover study.

Subjects: Twelve healthy male subjects were enrolled in the study.

Selection criteria, Exclusion criteria and Prohibitions: Please see Report #B-07143 above.

Dose and treatment:

Test product: A. 1x500 mg Cefaclor capsule (Biocraft), lot #52786, lot size capsules, administered following an overnight fast.
B. 1x500 mg Cefaclor capsule (Biocraft), lot #52786, administered within five minutes of a high fat breakfast preceded by an overnight fast.

Reference product: C. 1x500 mg Ceclor® Pulvule® (Lilly), lot #6PC28A, Exp. 12/95, administered within five minutes of a high fat breakfast preceded by an overnight fast.

Food an Fluid intake: Subjects on regimen A fasted overnight before dosing and for 4 hours thereafter. Subjects on regimen B and C fasted overnight until 15 minutes prior to dosing when a standard breakfast was administered. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 120 g of hashed browned potatoes, 180 mL of orange juice, and 240 mL of whole milk. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. A standard meal was provided at 4 hours after drug administration.

Washout period: One week between doses.

Blood collection: Blood samples were collected at 0 (pre-dose) and at the following times after dosing: 0.167, 0.333, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 4.5 and 5 hours.

Assay Methodology: Please see Report #B-07143 above.

Statistical Analysis:

AUCTLQC, AUCinf, Cmax, Kel, T1/2 were determined and the concentrations at each sampling time point were reported.

VI. In Vivo Results:

Twelve (12) subjects enrolled in the study and all subjects completed the entire study. There were no side effects observed, or events reported by the subjects, or noted by the staff.

The plasma concentrations and pharmacokinetic parameters of Cefaclor are summarized in Table II.

Table II

Mean Plasma Cefaclor Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x500 mg Cefaclor Capsules Under Fasting and Nonfasting Conditions
(N=12)

Time hr	Treatment A Biocraft Fasting Lot #52786 ug/mL (CV%)	Treatment B Biocraft Nonfasting Lot #52786 ug/mL (CV%)	Treatment C Lilly Nonfasting Lot #6PC28A ug/mL (CV%)
0	0	0	0
0.167	0	0	0
0.333	2.189(123.7)	0.026(346.4)	0.097(346.4)
0.500	6.580(99.7)	0.376(127.6)	0.299(266.9)
0.750	7.622(56.7)	1.251(101.8)	1.024(172.8)
1.000	7.183(35.8)	2.161(115.5)	1.650(90.7)
1.250	5.881(24.5)	3.426(77.3)	3.120(54.0)
1.500	4.207(46.5)	4.301(43.5)	3.987(36.8)
1.750	2.993(53.2)	4.132(24.4)	4.562(23.0)
2.000	2.239(55.8)	3.917(20.9)	4.252(27.4)
2.500	1.212(53.4)	3.448(15.3)	3.624(33.1)
3.000	0.769(44.9)	2.443(24.8)	2.587(28.2)
3.500	0.450(61.6)	1.701(36.2)	1.867(-36.8)
4.000	0.299(64.9)	1.200(39.7)	1.207(48.1)
4.500	0.162(125.7)	0.811(42.8)	0.829(52.9)
5.000	0.033(346.4)	0.522(46.3)	0.475(54.2)

				B/C
AUCTLQC (ug.hr/mL)	10.91(33.5)	10.30(21.8)	10.43(15.4)	0.99
AUCinf (ug.hr/mL)	11.58(25.0)	11.06(21.3)	11.05(14.7)	1.00
Cmax(ug/mL)	10.11(46.3)	4.91(37.3)	5.09(22.2)	0.96
Tmax (hr)	1.04(79.2)	1.69(19.1)	1.79(25.8)	
Kel(1/hr)	0.97(37.9)	0.79(21.0)	0.87(18.7)	
T1/2(hr)	1.19(142.5)	0.92(24.3)	0.82(19.0)	

1. For Biocraft's Cefaclor, the mean AUCTLQC and AUCinf values are almost the same as the AUCTLQC and AUCinf values for the reference product under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUCTLQC and AUCinf.

2. For the test product, the mean Cmax value is 3.5% lower than the reference product value under nonfasting conditions. The

ratio of the test mean to the reference mean is 0.96, which is within the acceptable range of 0.8-1.2 for Cmax.

3. Under nonfasting conditions, the mean Cmax for the test product decreased by 51.4%, whereas Tmax increased by 62.5% compared to fasting conditions, which are in agreement with results in the literature.

4. The Cefaclor plasma concentrations peaked at 1.5 and 1.75 hours for the test and reference products, respectively, under nonfasting conditions, and at 0.75 hour for the test product under fasting conditions.

VII. Formulations:

Biocraft's comparative formulations for its Cefaclor 250 mg and 500 mg capsules are shown below.

Cefaclor Capsules

List Of Components And Quantitative Composition

	250 MG Capsule MG/Capsule	**500 MG Capsule MG/Capsule**
Ingredients		
Cefaclor Monohydrate, USP		

g/mL.

VIII. In Vitro Dissolution Testing:

Method:	USP XXII apparatus II at 50 rpm
Medium:	900 mL water
Number of Capsules:	12
Test product:	Biocraft's Cefaclor 250 mg capsules, lot #52869 500 mg capsules, lot #52786

Reference product: Lilly's Ceclor® Pulvules®
250 mg, lot #7DT73A
500 mg, lot #6PC28A

Dissolution testing results are shown in Table III.

IX. Deficiency Comments:

1. On page #0196 of the Clinical Findings (Final Report) for Protocol #B-07143, the clinical facility has stated that " The plasma and urine samples for subject #25 were shipped on January 26, 1994 as replacement for subject #01, as requested by the analytical facility". The firm has included subject #1 in the analytical and the statistical reports of the study but not subject #25.
The firm should explain if this replacement took place and the reason for the replacement.

2. The firm should include all the assayed data for all subjects in the statistical evaluation of the study.

X. Comments:

1. The confidence intervals for LNAUCTLQC, LNAUCinf and LNCmax are within the acceptable range of 80-125%.
2. It should be noted that the 90% CI for LNCmax ranged from 97.8% to 125.0%
3. The in vitro dissolution testing for the test products 250 mg and 500 mg capsules is acceptable.
4. The formulation for Cefaclor 250 mg strength is proportionally similar to the 500 mg strength of the test product.
5. The assay method validation is acceptable.

XI. Recommendations:

1. The single-dose fasting bioequivalence study #B-07143, conducted by Biocraft Laboratories, Inc. on its Cefaclor 500 mg capsule, lot #52786, comparing it to Ceclor® 500 mg Pulvules® manufactured by Eli Lilly and Company has been found incomplete by the Division of Bioequivalence for reasons given in the deficiency comments 1 & 2.

2. The single-dose post-prandial bioequivalence study #B-10143 conducted by Biocraft Laboratories, Inc. on its Cefaclor 500 mg capsule, lot #52786, comparing it to Ceclor® 500 mg Pulvules® manufactured by Eli Lilly and Company has been found acceptable by the Division of Bioequivalence.

3. The firm's request for a waiver of bioequivalence study requirements for its Cefaclor 250 mg capsule is pending until the

bioequivalence study for the 500 mg strength of the test product is acceptable.

4. The dissolution testing conducted by Biocraft Laboratories, Inc. on its Cefaclor 500 mg capsules, lot #52786, and 250 mg capsules, lot #52869, comparing them with the respective strengths of Eli Lilly's Ceclor® Pulvules® 500 mg and 250 mg capsules is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water using USP XXII apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

The firm should be informed of the deficiency comments and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE /S/ Date: 8/8/94

/S/

Concur: _____ Date: 8/10/94
Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Cefaclor Capsules
Dose Strength: 250 mg & 500 mg
ANDA No.: 64-081
Firm: Biocraft Laboratories, Inc.
Submission Date: May 12, 1994
File Name: 64081SBW.595

I. Conditions for Dissolution Testing:

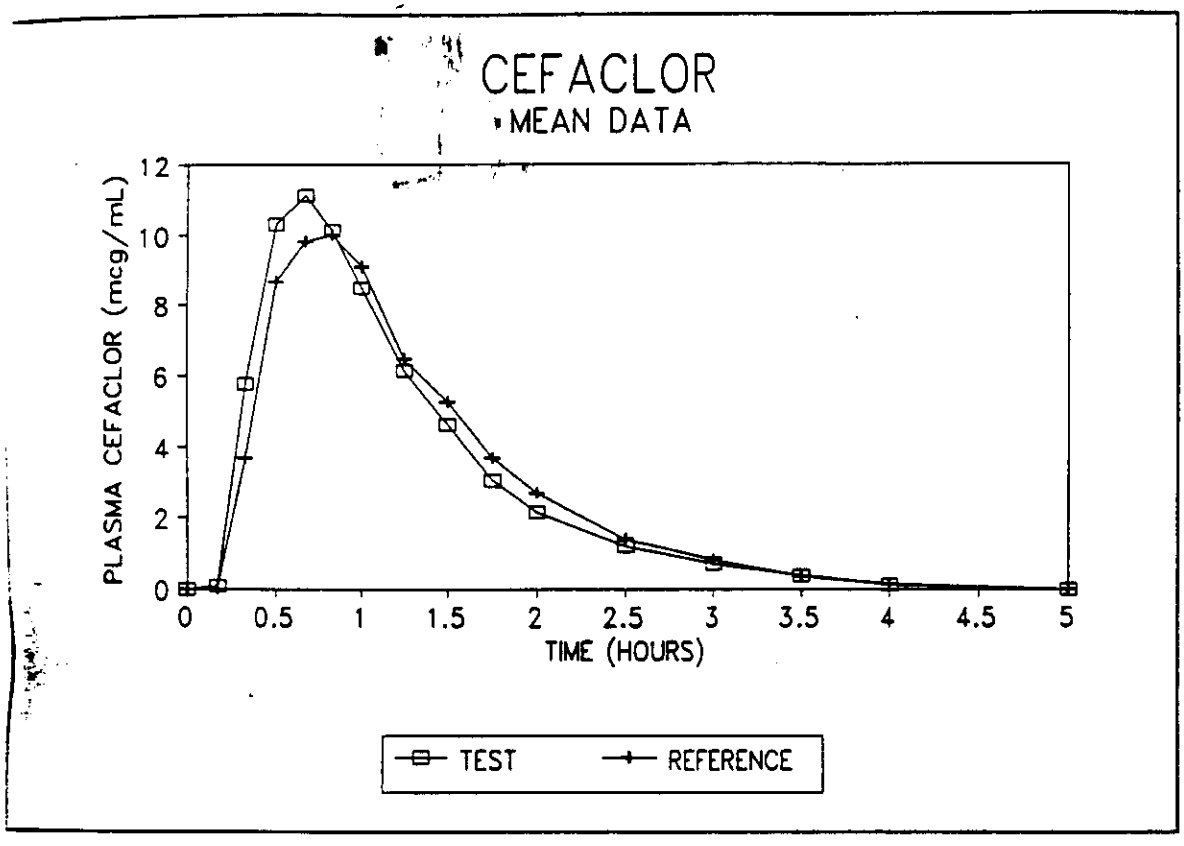
USP XXII Basket: X Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of water
Specifications:
Reference Drug: Ceclor (Lilly)
Assay Methodology:

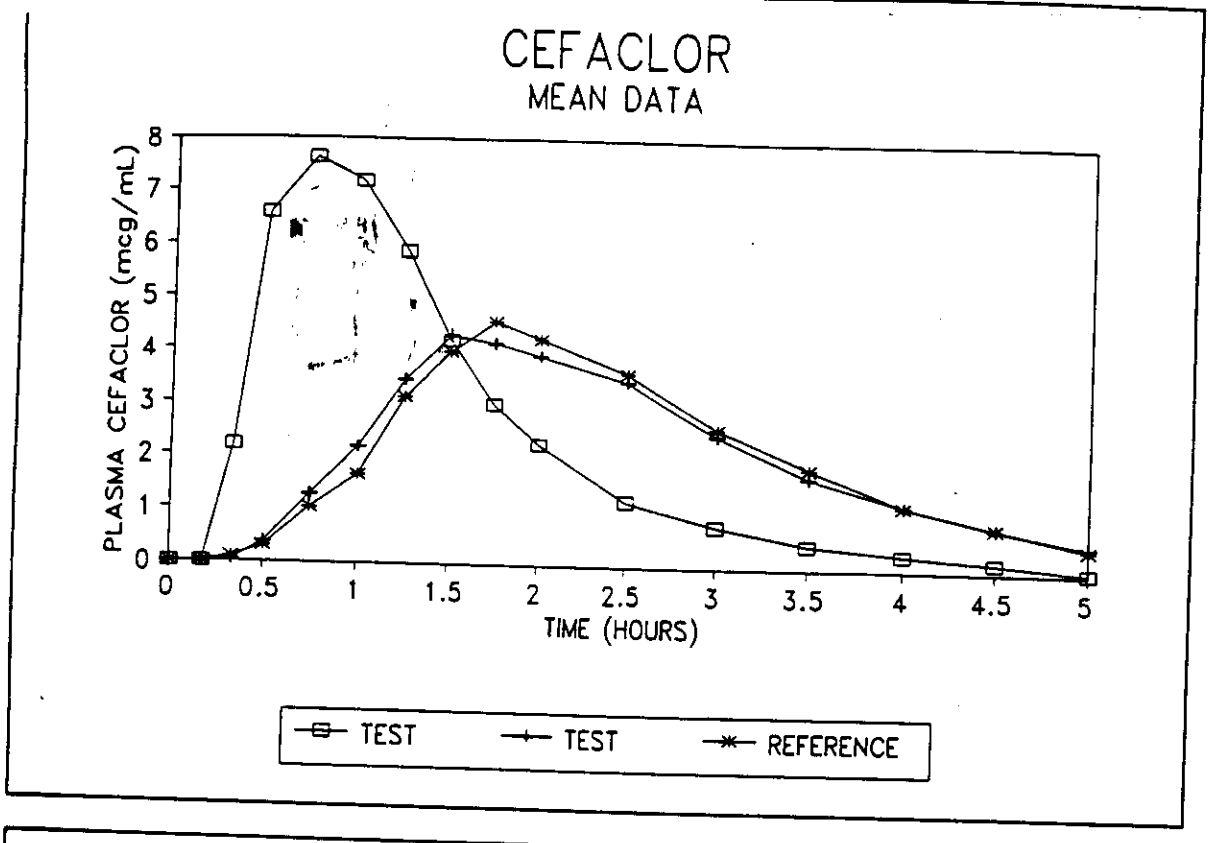
II. Results of In Vitro Dissolution Testing:

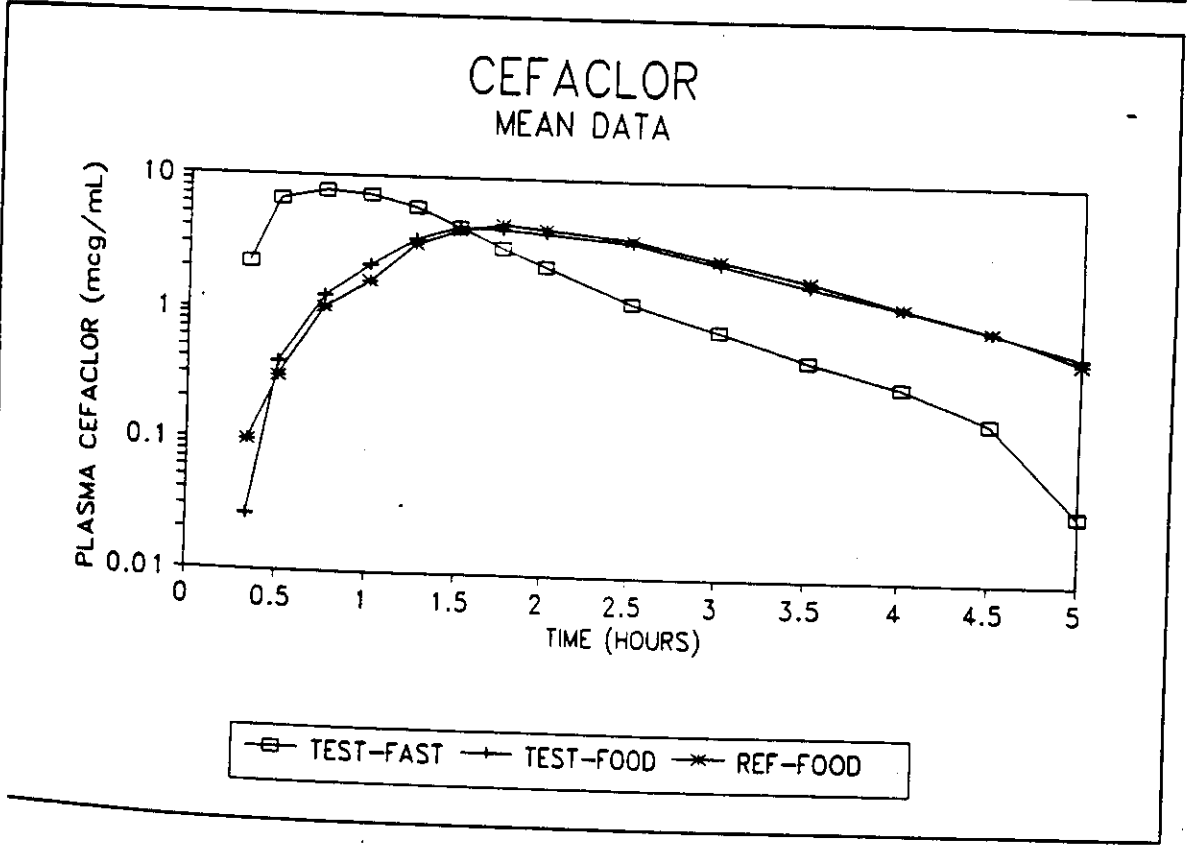
Sampling Times (Minutes)	Test Product Lot # 52869 Strength (mg) 250			Reference Product Lot # 7DT73A Strength (mg) 250		
	Mean %	Range	%CV	Mean %	Range	%CV
5	85.7		13.9	94.5		4.5
10	96.5		6.1	99.8		4.0
15	99.0		5.6	101.4		3.8
20	101.2		5.0	102.1		3.6
30	103.0		4.8	104.3		3.5

Sampling Times (Minutes)	Test Product Lot # 52786 Strength (mg) 500			Reference Product Lot #6PC28A Strength (mg) 500		
	Mean %	Range	%CV	Mean %	Range	%CV
5	65.3		11.9	68.1		17.6
10	81.6		7.1	84.6		9.1
15	85.5		5.4	87.4		8.0
20	87.6		5.0	89.4		7.1
30	90.5		4.3	95.3		4.4

Linear Plot of Mean Plasma Drug Concentration *vs* Time




CEFACLOR
MEAN DATA
PLASMA CEFACLOR (mcg/mL)
0
1
2
3
4
5
6
7
8
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
TIME (HOURS)
TEST
TEST
REFERENCE


CEFACLOR
MEAN DATA
PLASMA CEFACLOR (mcg/mL)
10
1
0.1
0.01
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
TIME (HOURS)
TEST-FAST
TEST-FOOD
REF-FOOD

MAY 25 1993

Cefaclor Capsules
250 mg and 500 mg
ANDA # 64-081
Reviewer: Moheb H. Makary
WP 64081SDW.293

Biocraft Laboratories, Inc.
Fair Lawn, NJ
Submission Date:
February 19, 1993

Review of Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has submitted in vivo bioequivalence study reports of fasting and nonfasting studies on its cefaclor 500 mg capsules and dissolution data to compare the test product with Lilly's Ceclor® 500 mg Pulvules®. The firm also submitted the formulations for its test products, 500 mg and 250 mg capsules, and their dissolution testing results.

II. Background:

Cefaclor is a cephalosporin antibiotic which inhibits bacterial cell-wall synthesis in a manner similar to that of penicillin. Cefaclor is used in the treatment of otitis media, lower and upper respiratory infections, urinary tract infections and skin and skin structure infections.

Cefaclor is well absorbed after oral administration in fasting subjects. Total absorption is similar regardless whether the drug is given with or without food; however, when it is taken with food, the peak concentration achieved is 50% to 75% of that observed in fasting subjects and generally appears about 1 hour later.

Following administration of 250 mg, 500 mg, and 1 g doses in fasting subjects, average peak serum levels of approximately 7, 13, and 23 ug/mL, respectively, were obtained within 30 to 60 minutes. Approximately 60% to 85% of the drug is excreted unchanged in urine within 8 hours, the major portion being excreted within the first 2 hours. The serum elimination half-life in subjects with normal renal function is 0.6 to 0.9 hour. In patients with severely reduced renal function, the plasma elimination half-life of the drug is 2.3 to 2.8 hours.

Currently, cefaclor is marketed by Eli Lilly under the name Ceclor®, 250 mg and 500 mg capsules, and as a powder for reconstitution as suspension for oral administration, 125 mg/5 mL, 187 mg/5 mL, 250 mg/5 mL and 375 mg/5 mL. The usual adult dosage is 250 mg every 8 hours. For more severe infections (such as pneumonia), doses may be doubled.

III. Report #90391 For Single-Dose, Two-Way Crossover Bioavailability Study of Cefaclor 500 mg Capsules Under Fasting Conditions:

Study site:

Investigators:

Study design:	Open-label, randomized, two-way crossover study.
Subjects:	Twenty-four healthy male volunteers were enrolled in the study. A total of twenty-three subjects completed the study.
Selection criteria:	The subjects were between 18 to 45 years of age. All subjects were within ± 15% of their ideal weights as described in the Metropolitan Life Insurance Company, 1983. Only healthy subjects with clinically normal laboratory profiles were enrolled in the study.
Exclusion criteria:	Consisted of hypersensitivity or idiosyncratic reaction to any drug, especially cephalosporin antibiotics or penicillin, cardiovascular, pulmonary, hepatic, renal, hematologic, dermatologic, neurologic or psychiatric disease.
Prohibitions:	Subjects were instructed not to take any drugs for the 7 days preceding the study and during the course of the study. Subjects were also instructed to abstain from alcohol, tea, coffee, chocolate and caffeine and xanthine containing products for 24 hours before dosing and throughout the period of sample collection.
Dose and treatment:	All subjects completed an overnight fast (10 hours) before any of the following drug treatments:
Test product:	A. 1x500 mg cefaclor capsule (Biocraft), lot

#52010, lot size capsules. Potency is 101.5%.

Reference product: B. 1x500 mg Ceclor® Pulvule® (Lilly), lot #5AG 48 A, Exp. 4/94. Potency is 101.2%.

Food and fluid intake: Following drug administration, the subjects remained fasting for 4 hours and then received a meal. Standard meals were provided at appropriate times thereafter. Water was permitted ad lib. until 2 hours before and 4 hours after dosing.

Blood collection: Blood samples (1x5 mL) were collected in Vacutainers containing EDTA at 0 (pre-dose) and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5 and 7 hours. Blood samples were cooled in an ice bath and centrifuged under refrigeration within 10 minutes of sample collection. Plasma samples were stored at - 80°C or lower, pending assay.

Urine collection: A pre-dose urine sample was obtained for each subject and all urine was collected over 0-7 hours interval. Each individual voiding was measured and 2 aliquots taken and frozen as soon as possible after collection.

Washout period: 96 hours

Assay Methodology:

Cefaclor was quantitated in human plasma by high performance liquid chromatography using UV detection. The method was developed and validated at Phoenix, Canada. Human plasma proteins were precipitated with an acidic solution containing internal standard. After centrifugation, the supernatant was injected into a HPLC system.

Sensitivity: The lowest non-zero standard was 0.2 ug/mL.

Recovery:
85.9% ±2.29 at 0.60 ug/mL (CV = 2.7% n = 6)
79.4% ±1.36 at 11.25 ug/mL (CV = 1.7% n = 6)
85.1% ±0.71 at 20.00 ug/mL (CV = 0.8% n = 6)

Specificity: Sample chromatograms of plasma spiked with cefaclor and the internal standard showed no interference from endogenous plasma constituents.

Precision: Between-batch precision for quality control samples ranged from 5.6% to 5.8%, and within-batch precision ranged from 1.2% to 2.7%.

Accuracy: Accuracy for quality control samples ranged from 92.7% to 102.4%.

Stability: Long Term Frozen: Stable at -80°C for at least 157 days (the study samples were stored frozen for 68 days).

Short Term: Stable on ice bath for at least 4.3 hours.

Freeze-thaw: Stable after three freeze-thaw cycles.

In the Autosampler: Stable at least 66 hours.

Statistical Analysis:

Statistical analysis was performed on cefaclor using the SAS with General Linear Models Procedure (GLM). Analysis of variance was performed on AUC(0-t), AUCinf, Cmax, Tmax, Kel, T1/2 and cefaclor concentrations at each sampling time point.

IV. In Vivo results:

Twenty-four healthy male volunteers enrolled in the study, subject #9 withdrew from the study for personal reasons prior to check-in for the period 2. A total of 23 subjects completed the study. Two subjects complained of dizziness, nausea and weakness. No medication was required for any complaint.

The plasma concentrations and pharmacokinetic parameters for cefaclor are summarized in Table I.

Table I

Mean Plasma Cefaclor Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 500 mg Capsule Under Fasting Conditions

(N=23)

Time hr	Biocraft Test Product Lot #52010 ug/mL (CV%)	Lilly Reference Product Lot #5AG 48 A ug/mL (CV%)
0	0	0
0.25	0.20(168.0)	0.25(252.1)
0.50	6.41(65.7)	8.52(77.1)
0.75	11.68(33.1)	13.19(39.8)
1	11.15(30.0)	12.35(33.8)
1.25	9.52(34.7)	9.22(29.6)
1.50	7.73(35.1)	6.56(38.6)
2	4.12(43.0)	3.91(50.8)
2.50	2.56(47.8)	2.39(67.7)
3	1.63(52.8)	1.27(42.8)
3.50	0.97(55.6)	0.79(57.4)
4	0.59(82.7)	0.55(47.4)
4.50	0.33(74.0)	0.30(66.7)
5.00	0.09(187.4)	0.12(123.7)
6	0.03(266.9)	0.00(-)
7	0	0

				Difference%	90% CI
AUC(0-t)	(ug.hr/mL)	17.75(17.8)	17.92(19.4)	- 0.95	93.5-104.8
AUCinf	(ug.hr/mL)	18.04(17.7)	18.21(19.2)	- 0.93	93.6-104.9
Cmax	(ug/mL)	13.46(23.3)	15.76(27.0)	-14.59	75.8- 95.7
Tmax	(hr)	0.90(27.4)	0.80(26.4)		
Kel	(1/hr)	1.05(16.2)	1.08(10.3)		
T1/2	(hr)	0.67(16.4)	0.65(10.2)		
LNAUC					94.1-104.8
LNAUCinf					94.2-104.8
LNCmax					78.0- 96.3

1. The reviewer noted that the cefaclor plasma levels peaked at 0.75 hour for the test and reference products under fasting conditions which is in agreement with the literature reported value of 0.75-1 hour for the reference product (Physicians's Desk Reference, 47th ed. 1993:1285-2).

2. For Biocraft's test product, the mean Cmax value is 14.6% lower than the reference product value and the 90% confidence interval is outside the acceptable range of 80-125% for the Cmax.

3. The AUC(0-t) and AUCinf values for the test product are almost the same as the AUC and AUCinf values for the reference product,

and the 90% confidence intervals are within the acceptable range of 80-125%

Statistical Evaluation:

There was a statistically significant difference between formulations for Cmax (p=0.0223).

V. Report #901743 For Post-Prandial Single-Dose Bioequivalence Study:

Objective:	The objective of this study was to compare the bioavailability of Biocraft 500 mg cefaclor capsules and Lilly's Ceclor® 500 mg Pulvules® under nonfasting conditions.
Study site:	
Investigators:	Please see Report #901391 above.
Study design:	Open-label, randomized, three-way crossover study.
Subjects:	Twelve healthy male subjects were enrolled in the study.
Selection criteria, Exclusion criteria and Prohibitions:	Please see Report #901391 above.
Dose and treatment:	
Test product:	A. 1x500 mg cefaclor capsule (Biocraft), lot #52010, lot size capsules, administered following an overnight fast. B. 1x500 mg cefaclor capsule (Biocraft), lot #52010, administered following a standard breakfast.
Reference product:	C. 1x500 mg Ceclor® Pulvule® (Lilly), lot #5AG 48 A, Exp. 4/94, administered following a standard breakfast.
Food an Fluid intake:	Subjects on regimen A fasted overnight before dosing and for 4 hours thereafter. Subjects on regimen B and C fasted overnight until 20 minutes prior to dosing when a standard breakfast was administered. The standard breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 120 g of

hashed browned potatoes, 180 mL of orange juice, and 240 mL of whole milk. Water was not permitted for 2 hours before and 4 hours after the dose, but was allowed at all other times. A standard meal was provided at 4 hours after drug administration.

Washout period: 72 hours between doses.

Blood collection: Blood samples were collected at 0 (pre-dose) and at the following times after dosing: 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, and 7 hours.

Assay Methodology: Please see Report #901391 above.

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 were determined and the concentrations at each sampling time point were reported.

VI. In Vivo Results:

Twelve (12) subjects enrolled in the study and eleven subjects completed the entire study. Subject #4, in period 1, at 1.5 hours after dosing (Lilly's Ceclor®) reported a mild case of itchy red spots on his left arm and on the back. The subject was examined by the medical director who concluded that the subject was experiencing a mild reaction to the study drug and was subsequently withdrawn from the study prior to period 2. Several complaints of headache, dizziness, and cold sweat were reported. All these reactions were judged to be unrelated to the study drugs by the medical director.

The plasma concentrations and pharmacokinetic parameters of cefaclor are summarized in Table II.

Table II

Mean Plasma Cefaclor Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 1x500 mg Cefaclor Capsules Under Fasting and Nonfasting Conditions

(N=11)

Time hr	Treatment A Biocraft Fasting Lot #52010 ug/mL (CV%)	Treatment B Biocraft Nonfasting Lot #52010 ug/mL (CV%)	Treatment C Lilly Nonfasting Lot #5AG 48 A ug/mL (CV%)
0	0	0	0
0.25	0.53(166.7)	0	0.40(331.7)
0.50	6.80(66.7)	0.22(174.1)	2.90(189.9)
0.75	10.37(50.7)	2.72(123.0)	4.97(126.0)
1.00	9.24(30.6)	4.23(68.5)	4.88(96.8)
1.25	8.07(21.2)	6.87(59.5)	5.37(60.7)
1.50	5.54(25.3)	5.51(45.5)	5.23(31.9)
2.00	3.51(43.4)	5.41(36.0)	5.37(48.8)
2.50	2.18(58.6)	4.92(39.0)	4.35(46.7)
3.00	1.38(71.1)	3.79(58.0)	2.83(58.4)
3.50	0.84(82.6)	2.20(66.1)	1.70(56.8)
4.00	0.53(86.4)	1.42(67.3)	1.11(53.6)
4.50	0.23(101.1)	0.74(52.4)	0.65(65.1)
5.00	0.10(163.6)	0.39(82.4)	0.28(95.8)
6.00	0	0.05(225.0)	0.02(331.7)
7.00	0	0	0

				B/C
AUC(0-t) (ug.hr/mL)	15.14(16.3)	14.82(12.4)	14.65(19.4)	1.01
AUCinf (ug.hr/mL)	15.42(16.3)	15.23(12.7)	15.00(19.2)	1.02
Cmax(ug/mL)	12.13(29.8)	8.88(35.2)	9.88(39.4)	0.90
Tmax (hr)	0.89(29.2)	1.55(39.5)	1.64(46.5)	
Kel(1/hr)	1.11(11.7)	1.04(12.2)	1.07(17.8)	
T1/2(hr)	0.63(11.6)	0.68(15.3)	0.67(17.8)	

1. For Biocraft's cefaclor, the mean AUC(0-t) and AUCinf values are 1.2% and 1.5% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t) and AUCinf.

2. For the test product, the mean Cmax value is 10.1% lower than the reference product value under nonfasting conditions. The ratio of the test mean to the reference mean is 0.90, which is within the acceptable range of 0.8-1.2 for Cmax.

3. The reviewer noted that under nonfasting conditions, the mean Cmax for the test product decreased by 27%, whereas Tmax increased by 74% compared to fasting conditions, which are in agreement with results in the literature.

4. The cefaclor plasma concentrations peaked at 1.25 hour for both test and reference products under nonfasting conditions, and at 0.75 hour for the test product under fasting conditions.

VII. Formulations:

Biocraft's comparative formulations for its cefaclor 250 mg and 500 mg capsules are shown below.

Cefaclor Capsules

List Of Components And Quantitative Composition

	250 MG Capsule MG/Capsule	**500 MG Capsule MG/Capsule**
Ingredients		
Cefaclor Monohydrate, USP		**
(		
Totals		
*		

VIII. In Vitro Dissolution Testing:

Method:	USP XXII apparatus I at 100 rpm
	USP XXII apparatus II at 100 rpm
Medium:	900 mL water
	900 mL 0.1N HCl
	900 mL phosphate buffer pH 4.5
Number of Capsules:	12
Test product:	Biocraft's cefaclor
	250 mg capsules, lot #52064
	500 mg capsules, lot #52010
	500 mg capsules, lot #52010A
Reference product:	Lilly's Ceclor® Pulvules®
	250 mg, lot #4MF11A
	500 mg, lot #5AG48A

Dissolution testing results are shown in Table III.

IX. Deficiency Comment:

For cefaclor, a statistically significant difference between the firm's test product and the reference product was observed for Cmax under fasting conditions. The least square means for Cmax value was 14.2% lower for the test product than for the reference product. The Biocraft study results, therefore, suggest that the test product (Biocraft) has a slower rate of absorption when compared to that of the reference product under fasting conditions and the 90% confidence interval for Cmax was not within the acceptable range of 80-125%.

X. Comments:

1. The firm's in vivo bioequivalence study under fasting conditions is not acceptable. The 90% confidence interval is outside the acceptable range for Cmax.
2. The confidence interval for AUC(0-t) and AUCinf is within the acceptable range of 80-125%.
3. The firm's in vivo post-prandial bioequivalence study is acceptable. Subject #4 withdrew from the study prior to period 2 due to the adverse reaction to the study drug.
4. The in vitro dissolution testing for the test products 250 mg and 500 mg capsules is acceptable.
5. The formulation for cefaclor 250 mg strength is proportionally similar to the 500 mg strength of the test product.
6. The assay method validation is acceptable.
7. Several complaints of dizziness, nausea, weakness and headache were judged to be unrelated to the study drugs by the medical director. One subject experienced a mild reaction to the study drug and withdrew from the post-prandial study.

XI. Recommendations:

1. The single-dose fasting bioequivalence study #901391, conducted by Biocraft Laboratories, Inc. on its cefaclor 500 mg capsule, lot #52010, comparing it to Ceclor® 500 mg Pulvules® manufactured by Eli Lilly and Company has been found unacceptable by the Division of Bioequivalence for reasons given in the deficiency comment.

2. The single-dose post-prandial bioequivalence study #901743 conducted by Biocraft Laboratories, Inc. on its cefaclor 500 mg capsule, lot #52010, comparing it to Ceclor® 500 mg Pulvules® manufactured by Eli Lilly and Company has been found acceptable by the Division of Bioequivalence.

3. The firm's request for a waiver of bioequivalence study requirements for its cefaclor 250 mg capsule can not be granted since the bioequivalence study for the 500 mg cefaclor capsule under fasting conditions is unacceptable.

4. The dissolution testing conducted by Biocraft Laboratories, Inc. on its cefaclor 500 mg capsules, lot #52010, and 250 mg capsules, lot #52064, comparing them with the respective strengths of Eli Lilly's Ceclor® Pulvules® 500 mg and 250 mg capsules is acceptable. However the firm needs to resubmit the waiver request following completion of acceptable fasting study.

The firm should be informed of the deficiency comment and recommendations.

/S/

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED MPARK
FT INITIALLED MPARK

M.P.M. /S/ Date: 5/18/93

/S/

Concur: _____ Date: 5/22/93
Ramakant M. Mhatre, Ph.D.
Acting Director
Division of Bioequivalence

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Cefaclor Capsules
Dose Strength: 250 mg & 500 mg
ANDA No.: 64-081
Firm: Biocraft Laboratories, Inc.
Submission Date: February 19, 1993
File Name: 64081SDW.293

I. Conditions for Dissolution Testing:

USP XXII Basket: X Paddle: X RPM: 100
No. Units Tested: 12
Medium: 900 mL of water, 0.1N HCl or phosphate buffer pH 4.5
Specifications:
Reference Drug: Ceclor (Lilly)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 52064 Water Strength(mg) 250 Basket			Reference Product Lot # 4MF11A Water Strength(mg) 250 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	102.3		5.3	102.3		1.5
30	106.7		3.5	101.8		1.9
45	106.3		2.2	102.0		1.7

Sampling Times (Minutes)	Test Product Lot # 52064 0.1N HCl Strength(mg) 250 Basket			Reference Product Lot # 4MF11A 0.1N HCL Strength(mg) 250 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	97.9		7.2	103.3		3.3
30	104.7		4.1	103.2		2.8
45	105.3		3.2	104.1		3.0

Sampling Times (Minutes)	Test Product Lot #52010 Water Strength(mg)500 Basket			Reference Product Lot #5AG48A Water Strength(mg)500 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	90.72		2.6	104.35		1.1
30	98.87	2	2.2	104.09		1.0
45	100.05		2.2	103.36		1.0
60	100.12		2.0	102.90		0.8

Sampling Times (Minutes)	Test Product Lot #52010A Water Strength(mg)500 Basket			Reference Product Lot #5AG48A Water Strength(mg)500 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	90.4		10.2	104.4		1.1
30	101.8		2.5	104.1		1.0
45	101.7		1.6	103.4		1.0
60				103.0		0.8

Sampling Times (Minutes)	Test Product Lot #52010A 0.1N HCl Strength(mg)500 Basket			Reference Product Lot #5AG48A 0.1N HCl Strength(mg) 500 Paddle		
	Mean %	Range	%CV	Mean %	Range	%CV
10				97.0		2.0
15	91.8		4.7			
20				99.5		1.2
30	96.3		2.3	100.7		2.4
40				100.3		0.6
45	98.0		1.2			
60				99.6		1.0

Sampling Times (Minutes)	Test Product Lot # 52010 0.1N HCL Strength(mg)500 Basket			Reference Product Lot #5AG48A 0.1N HCl Strength(mg)500 Paddle		
	Mean %	Range	%CV	Mean %	Range	%CV
10				96.0		2.0
15	88.8		6.4			
20				99.5		1.2
30	98.7		3.8	100.7		2.4
40				100.3		0.6
45	103.0		3.0			
60	104.2		2.7	99.6		1.0

Sampling Times (Minutes)	Test Product Lot #52010 pH 4.5 buffer Strength(mg) 500			Reference Product Lot #5AG48A pH 4.5 buffer Strength(mg)500 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	91.5		4.9	102.1		2.2
30	97.2		3.1	101.5		2.4
45	97.3		3.0	100.8		2.7
60	96.3		2.8	100.4		2.6

Sampling Times (Minutes)	Test Product Lot #52064 pH 4.5 buffer Strength(mg)250 Basket			Reference Product Lot #4MF11A pH 4.5 buffer Strength(mg) 250 Basket		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.3		6.8	107.9		3.0
30	103.5		2.9	108.4		3.3
45	102.3		3.3	107.3		3.0

Figure 2

Project No. 901391

Mean Plasma Cefaclor Concentrations

(Linear Plot)

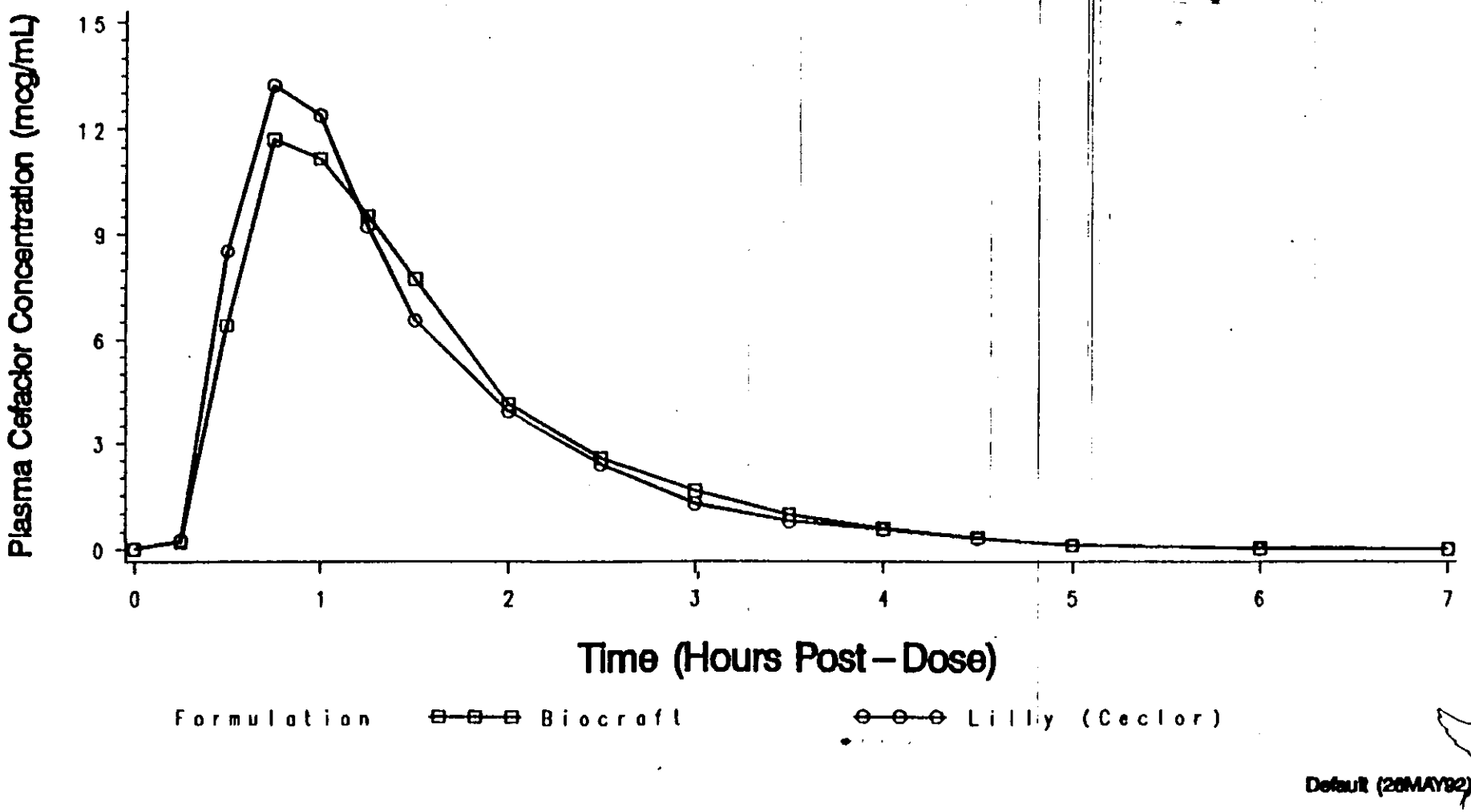
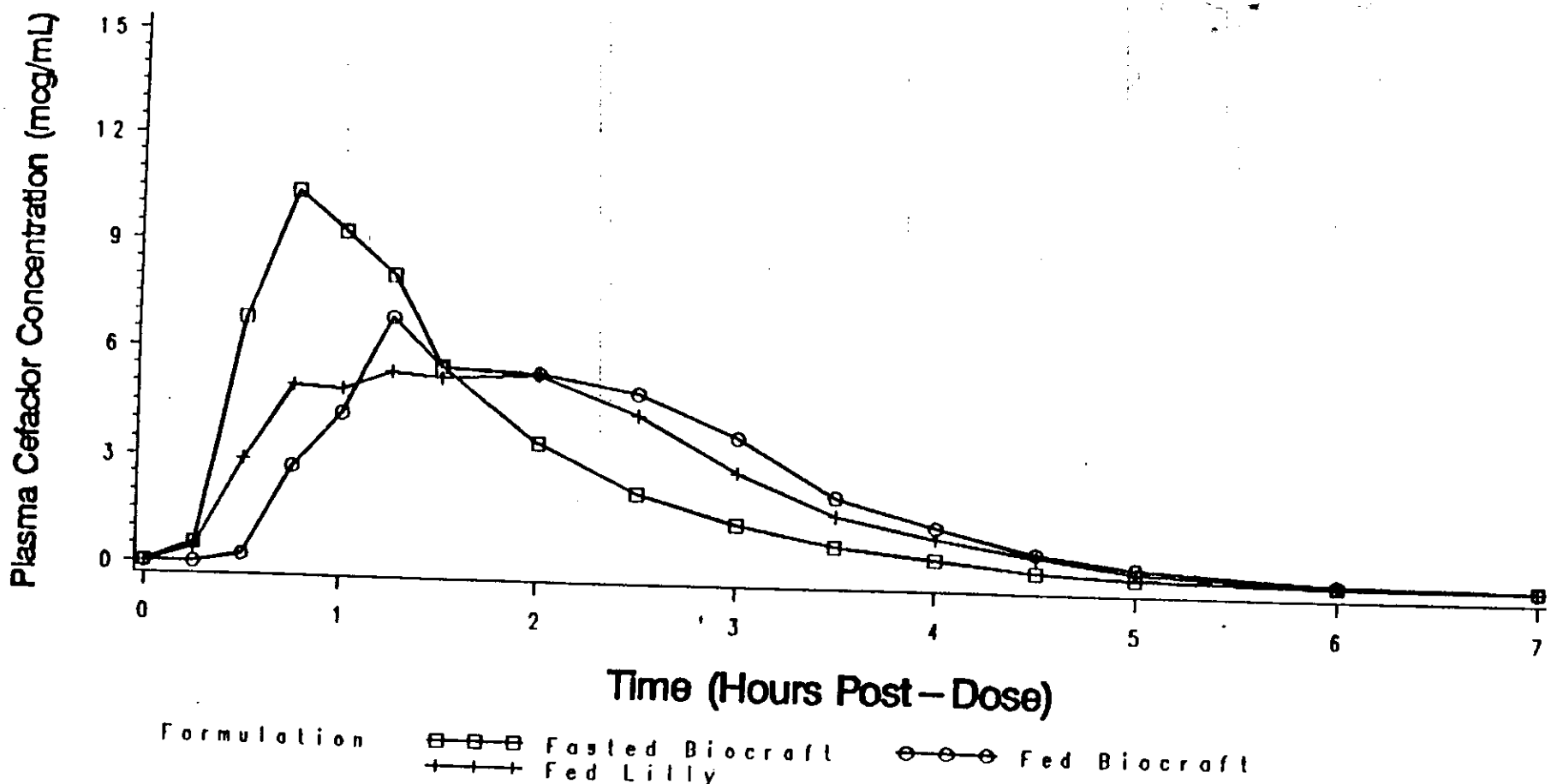


Figure 2

Project No. 901743

Mean Plasma Cefaclor Concentrations

(Linear Plot)



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February 19, 1993

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Rockville, Maryland 20855

RE: AADA
CEFACLOR CAPSULES, USP, 250 mg and 500 mg

Dear Staff:

Enclosed please find in duplicate, Biocraft's Abbreviated Antibiotic Drug Application (AADA) for Cefaclor Capsules, USP, 250 mg and 500 mg.

Three (3) copies of the Methods Validation Section for both the active ingredient and finished product have been attached, along with two (2) copies of the Bioequivalence Review Section.

Four (4) copies of the draft printed container labels, and four (4) copies of the draft printed package insert, have been affixed to the duplicate copies of this Submission. We have also attached copies of the labels and package insert from Ceclor®, brand of Cefaclor Capsules currently marketed in the United States by Eli Lilly Industries, Inc. Ceclor® has been approved for safety and effectiveness under Section 505 of the Federal Food, Drug and Cosmetic Act. Accordingly, Ceclor® is listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations", 12th Edition, and is hereinafter referred to as a "listed drug".

In order to satisfy the requirements of an Abbreviated Antibiotic Drug Application, we have included the following:

1. Information to show that the condition of use prescribed, recommended, or suggested in the labeling proposed for the drug for which the applicant seeks approval have been previously approved for the "listed drug". The attached copies of the labels and package insert of the "listed drug" indicate that they are identical to those proposed by Biocraft in its AADA.

2. The drug for which this applicant seeks approval has only one active ingredient. This ingredient is the same as that of the "listed drug."

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3. Information to show that the dosage form, the route of administration and strengths of the drug for which the applicant seeks approval, are the same as those of the "listed drug."

4. Information to show that Biocraft's proposed labeling is the same as the labeling approved for the "listed drug," except for changes that are necessary due to a change in manufacturer. The enclosed Biocraft labeling, as well as that of the "listed drug," show that they are identical.

   Side by side comparisons of container labels and package inserts of both Biocraft's and Eli Lilly's products, have all the differences identified and highlighted. Additionally, a separate explanation of these side by side differences is included in this Submission.

In-vivo Bioavailability Studies were performed on the 500 mg strength of Cefaclor Capsules, USP by]

The results of this biostudy are included in this Submission.

Biocraft hereby requests a Waiver from conducting an in-vivo Bioavailability study on Cefaclor Capsules, USP, 250 mg. strength. The 500 mg strength used in the bioavailability study is a very sensitive predicator of the bioavailability of the 250 mg strength because Biocraft's Cefaclor Capsules, USP, 250 mg and 500 mg are dose proportional in their active and inactive ingredients.

Additionally, as required under the Generic Drug Enforcement Act of 1992, Section 306(k)(1)(2), we have included Debarment Certifications in Section III of this Application. These Debarment Certifications include those from Biocraft Laboratories, Inc., and]

Thank you.

Sincerely,

BIOCRAFT LABORATORIES, INC.

Nora Buenviaje
Regulatory Associate

NB/pd
Enclosures